PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 725349	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/AU2004/001031	International filing date *(day/month/year)* 3 August 2004	Priority date *(day/month/year)* 13 August 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl. ***A61K 38/21*** (2006.01) ***A61K 31/7056*** (2006.01)
A61K 31/7052 (2006.01) ***A61P 31/12*** (2006.01)

Applicant

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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of **4** sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **5** sheets, as follows:
      [X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
9 June 2005	25 November 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **SHUBHRA CHANDRA** Telephone No. (02) 6283 2264

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001031

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☐ The international application in the language in which it was filed

☐ A translation of the international application into , which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3(a) and 23.1 (b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages **1-16** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☒ the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **17-21** received by this Authority on **9 June 2005** with the letter of **9 June 2005**
pages* received by this Authority on with the letter of

☐ the drawings:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing *(specify)*:
☐ any table(s) related to the sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing *(specify)*:
☐ any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-23	YES
	Claims	24-33	NO
Inventive step (IS)	Claims	1-23	YES
	Claims	24-33	NO
Industrial applicability (IA)	Claims	1-33	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

D1 WO 2000/023455 A1

D2 WO 2000/023454 A1

D3 WO 2001/081359 A1

D4 EP 1136075 B1

D5 WO 2000/062799 A1

D6 WO 2000/037110 A2

D7 WO 2002/032414 A2

D8 US 6172046 B1

D9 US 6472373 B1

D10 WO 2003/028755 A1

D11 EP 1317929 A2

D12 EP 0903148 B1

D13 EP 0956861 B1

D14 Craxi Antonio and Licata Anna, Clinical trial results of peginterferons in combination with ribavirin, Seminars in liver disease, 2003, 23 suppl1 35-46.

D15 Poynard T et al, Treatment and prevention of hepatitis C, La revue du praticien, 2000, 50 (10) 1100-1107.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of :Box V

Novelty (N) and Inventive Step (IS) Claims 1-23

None of the above mentioned documents discloses or fairly suggests the method of treating viral infections in a patient which method comprises the co-administration of interferon and a slow release formulation of Ribavirin.

Therefore, the invention defined in claims 1-23 is novel and inventive.

Novelty (N) Claims 24-33

D1- D3 disclose Ribavirin-interferon alfa combination therapy for eradicating detectable HCV-RNA in patients having Chronic Hepatitis C infection. All these citations disclose that the amount of the esters of ribavirin administered concurrently with the pegylated interferon-alfa is from 200-1600 mg per day. The lower end of this range falls within the scope of these claims**Error! Bookmark not defined.**.

Please note that claims 24-32 and 33 define a kit and composition respectively comprising interferon and ribavirin. These claims are defined by their ingredients not by the way they are administered into the patients.

Therefore the invention defined in claims 24-33 is not novel in the light of the documents D1-D3.

Inventive Step(IS) Claims 24-33

Claims 24-32 merely define a kit of known components (interferon and ribavirin), functioning in their normal way and not producing any obvious working relationship.

Therefore, claims 24-32 lack an inventive step.

Claim 33 defines a composition comprising interferon and ribavirin. These compositions are known from D1-D3 as explained above.

Therefore, claim 33 lacks an inventive step.

Industrial Applicability (IA) Claims 1-33

Claims 1-33 are industrially applicable.

Claims:

1. A method of treating viral infections in a patient which method comprises co-administering to said patient a therapeutically effective amount of interferon and ribavirin wherein at least said ribavirin is administered in a slow-release formulation to provide a clinically effective blood level in the portal vein and less than required to provide a clinically effective blood level in the peripheral circulation to thereby provide a dose-delivery rate having a selective antiviral and interferon potentiating effect in the liver.

2. The method according to claim 1, wherein the slow-release formulation releases ribavirin by a mechanism chosen from diffusion and erosion.

3. The method according to claim 1, wherein the slow-release formulation of ribavirin comprises at least one of polymer-coated multiparticulates, polymer-coated tablets, polymer-coated minitablets, and hydrophilic matrix tablets.

4. The method according to claim 1, wherein the ribavirin dose from 5 to 800 mg/day.

5. A method according to claim 4, wherein the ribavirin dose is less than 400 mg/day.

6. A method according to claim 5, wherein the ribavirin dose is in the range of from 20 to 350 mg/day.

7. A method according to claim 1, wherein the ribavirin dose is varied according to the body weight of the patient.

8. A method according to claim 7, wherein the ribavirin dose is less than 6 mg/kg/day.

9. A method according to claim 8, wherein the ribavirin dose is less than 5 mg/kg/day.

10. A method according to claim 9, wherein the ribavirin dose is in the range of from 1 to 5 mg/kg/day.

11. The method according to claim 10, wherein the viral infection is hepatitis C.

12. The method according to claim 1, wherein the ribavirin is in the form of at least one of a ribavirin ester, salt, or analogue of ribavirin shown to be effective as an antiviral agent.

13. The method according to claim 12, wherein the interferon is interferon alfa or pegylated interferon alfa.

14. The method of claim 13, wherein the interferon is interferon alfa 2b.

15. The method according to claim 14, wherein the interferon is administered parenterally.

16. The method according to claim 15, wherein the interferon is administered by subcutaneous IV or IM injection.

17. The method according to claim 16, wherein the interferon is administered parenterally in an amount of from 2 to 10 million IU per

week on a weekly, thrice weekly ("TIW"), every other day ("QOD") or daily basis.

18. The method according to claim 13, wherein the pegylated interferon alfa is pegylated interferon alfa-2b and is administered systemically in an amount of 0.5 to 2.0 micrograms per kilogram of body weight per week on a weekly, TIW, QOD or daily basis.

19. The method according to claim 13, wherein the pegylated interferon alfa is pegylated interferon alfa-2a and is administered systemically in an amount of 20 to 250 micrograms per kilogram of body weight per week on a weekly, TIW, QOD or daily basis.

20. A method according to claim 1 further comprising co-administering an antioxidant or other membrane protective agent which is administered in systemic doses.

21. A method according to claim 20 further comprising an antioxidant or other membrane protective agent which is administered as a low-dose, slow-release formulation.

22. A method according to claim20, further comprising an antioxidant or other membrane protective agent which is co-formulated with the ribavirin as a low-dose, slow-release formulation.

23. A use of a therapeutically effective amount of interferon with a low dose of ribavirin as a slow release formulation of said low dose of ribavirin as a slow release formulation being sufficient to provide a clinically effective blood level in the portal vein and less than required to provide a clinically effective level in the peripheral circulation and optionally an

antioxidant or other membrane protective agent in the preparation of a medicament to treat viral infections in a patient.

24. A kit for use in the treatment of viral infections comprising a therapeutically effective amount of interferon in combination with ribavirin and optionally an antioxidant or other membrane protective agent as a slow-release formulation wherein the kit comprises unit doses of ribavirin providing a dose delivery rate sufficient to provide a clinically effective blood level in the portal vein and less than required to provide a clinically effective blood level in the peripheral circulation to thereby provide a dose-delivery rate having a selective antiviral and interferon potentiating effect in the liver.

25. A kit according to claim 24 wherein the low-dose of ribavirin is administered in a slow-release formulation to provide a clinically effective blood level in the portal vein and less than required to provide a clinically effective blood level in the peripheral circulation.

26. A kit according to claim 24 wherein the slow-release formulation of ribavirin comprises at least one of polymer-coated multiparticulates, polymer-coated tablets, polymer-coated minitablets, and hydrophilic matrix tablets.

27. A kit according to claim 24 wherein the unit dose of ribavirin is less than 400 mg/day.

28. A kit according to claim 24 wherein the unit dose of ribavirin is less than 6 mg/kg/day.

29. A kit according to claim 24 wherein the ribavirin is in the form of at least one of a ribavirin ester, salt or analogue or ribavirin shown to be effective as an antiviral agent.

30. A kit according to claim 24 wherein the interferon is in a form for parenteral administration.

31. A kit according to claim 24 comprising unit doses of interferon for providing an amount of from 2 to 10 million IU per week by thrice weekly ("TIW"), every other day ("QOD") or daily administration.

32. A kit according to claim 24 wherein the interferon is interferon alfa or pegylated interferon alfa.

33. A unit dose of a pharmaceutical composition for the treatment of viral infections in a patient comprising a therapeutically effective amount of interferon together with a low dose of ribavirin and optionally an antioxidant or other membrane protective agent wherein the unit dose provides a dose delivery of ribavirin sufficient to provide a clinically effective blood level in the portal vein and less than required to provide a clinically effective blood level in the peripheral circulation.